PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 08 February 2001 (08.02.01)	
International application No. PCT/EP00/03551	**Applicant's or agent's file reference** 1805PTWO
International filing date (day/month/year) 19 April 2000 (19.04.00)	**Priority date** (day/month/year) 21 April 1999 (21.04.99)
Applicant CORVI MORA, Paolo et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

16 November 2000 (16.11.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Juan Cruz Telephone No.: (41-22) 338.83.38

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

PCT/EP 0 0 / 0 3 5 5 1

International Application No.

19 APR 2000

International Filing Date (19. 04. 2000)

EUROPEAN PATENT OFFICE

PCT INTERNATIONAL APPLICATION

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* 1805PTWO

Box No. I TITLE OF INVENTION

SALTS OF ASIATIC AND MADECASSIC ACID SUITABLE FOR THE PREPARATION OF PHARMACEUTICAL AND COSMETIC COMPOSITIONS

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

EUPHAR GROUP S.r.l.
Via Settala 3
20124 MILAN - ITALY

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State *(that is, country)* of nationality: IT

State *(that is, country)* of residence: IT

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

CORVI MORA Paolo
Via Scalabrini 49
29100 PIACENZA - ITALY

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: IT

State *(that is, country)* of residence: IT

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

GERVASI Gemma
NOTARBARTOLO & GERVASI S.p.A.
Corso di Porta Vittoria 9
20122 MILAN - ITALY

Telephone No. +39 02541799.1

Facsimile No. +39 0254179920

Teleprinter No.

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Sheet No. 2

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

RANISE Angelo
Via Borzone 21/13
16132 GENOVA - ITALY

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: IT

State *(that is, country)* of residence: IT

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [ ] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [ ] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [ ] the United States of America only
- [ ] the States indicated in the Supplemental Box

- [ ] Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

☒ **AP** **ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT

☒ **EA** **Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Conventi n and of the PCT

☒ **EP** **European Patent:** AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☒ **OA** **OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

☒ **AE** United Arab Emirates
☒ **AL** Albania .....
☒ **AM** Armenia .....
☒ **AT** Austria .....
☒ **AU** Australia .....
☒ **AZ** Azerbaijan
☒ **BA** Bosnia and Herzegovina .....
☒ **BB** Barbados
☒ **BG** Bulgaria .....
☒ **BR** Brazil .....
☒ **BY** Belarus .....
☒ **CA** Canada
☒ **CH** and **LI** Switzerland and Liechtenstein
☒ **CN** China .....
☒ **CR** Costa Rica .....
☒ **CU** Cuba .....
☒ **CZ** Czech Republic .....
☒ **DE** Germany .....
☒ **DK** Denmark .....
☒ **DM** Dominica
☒ **EE** Estonia .....
☒ **ES** Spain .....
☒ **FI** Finland .....
☒ **GB** United Kingdom
☒ **GD** Grenada
☒ **GE** Georgia .....
☒ **GH** Ghana .....
☒ **GM** Gambia
☒ **HR** Croatia .....
☒ **HU** Hungary .....
☒ **ID** Indonesia
☒ **IL** Israel .....
☒ **IN** India .....
☒ **IS** Iceland
☒ **JP** Japan .....
☒ **KE** Kenya .....
☒ **KG** Kyrgyzstan .....
☒ **KP** Democratic People's Republic of Korea .....
☒ **KR** Republic of Korea .....
☒ **KZ** Kazakhstan .....
☒ **LC** Saint Lucia
☒ **LK** Sri Lanka
☒ **LR** Liberia
☒ **LS** Lesotho .....
☒ **LT** Lithuania
☒ **LU** Luxembourg
☒ **LV** Latvia
☒ **MA** Morocco .....
☒ **MD** Republic of Moldova .....
☒ **MG** Madagascar .....
☒ **MK** The former Yugoslav Republic of Macedonia .....
☒ **MN** Mongolia
☒ **MW** Malawi .....
☒ **MX** Mexico .....
☒ **NO** Norway
☒ **NZ** New Zealand .....
☒ **PL** Poland .....
☒ **PT** Portugal .....
☒ **RO** Romania
☒ **RU** Russian Federation .....
☒ **SD** Sudan
☒ **SE** Sweden
☒ **SG** Singapore
☒ **SI** Slovenia .....
☒ **SK** Slovakia .....
☒ **SL** Sierra Leone .....
☒ **TJ** Tajikistan .....
☒ **TM** Turkmenistan .....
☒ **TR** Turkey .....
☒ **TT** Trinidad and Tobago .....
☒ **TZ** United Republic of Tanzania
☒ **UA** Ukraine .....
☒ **UG** Uganda .....
☒ **US** United States of America .....
☒ **UZ** Uzbekistan .....
☒ **VN** Viet Nam .....
☒ **YU** Yugoslavia .....
☒ **ZA** South Africa .....
☒ **ZW** Zimbabwe .....

Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet:

☒ DZ Algeria .....
☒ AG Antigua and Barbuda .....

Precautionary Designation Statement: In additi n to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which w uld be permitted under the PCT except any designati n(s) indicated in the Supplemental Box as being excluded from the scope f this statement. The applicant declares that those additional designati ns are subject to confirmation and that any designation which is n t confirmed before the expiration of 15 months from the priority date is t be regarded as withdrawn by the applicant at the expiration f that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

Box No. VI · PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box.

	Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1)	21. 04. 99 / 21 April 1999	MI99A000835	ITALY		
item (2)					
item (3)					

☐ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): _____

** Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)* : ISA /

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):*
Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets:**

request	:	4
description (excluding sequence listing part)	:	15
claims	:	1
abstract	:	1
drawings	:	1
sequence listing part of description	:	
Total number of sheets	:	22

This international application is **accompanied by** the item(s) marked below:

1. ☐ fee calculation sheet
2. ☒ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☒ other *(specify)*: accompanying letter

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: ENGLISH

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

GERVASI Gemma

Milan, 13 April 2000

For receiving Office use only

1. Date of actual receipt of the purported international application:	19. 04. 00 / 19 APR 2000	2. Drawings: ☒ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:		
4. Date of timely receipt of the required corrections under PCT Article 11(2):		
5. International Searching Authority (if two or more are competent): ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid.	

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

PATENT COOPERATION TREATY

PCT

INFORMATION CONCERNING ELECTED OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

From the INTERNATIONAL BUREAU

To:

GERVASI, Gemma
Notarbartolo & Gervasi S.p.A.
Corso di Porta Vittoria, 9
I-20122 Milano
ITALIE

Date of mailing (day/month/year) 08 February 2001 (08.02.01)	
Applicant's or agent's file reference 1805PTWO	**IMPORTANT INFORMATION**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/EP00/03551	19 April 2000 (19.04.00)	21 April 1999 (21.04.99)

Applicant
EUPHAR GROUP S.R.L. et al

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

   AP :GH,GM,KE,LS,MW,SD,SL,SZ,TZ,UG,ZW
   EP :AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE
   National :AU,BG,CA,CN,CZ,DE,IL,JP,KP,KR,MN,NO,NZ,PL,RO,RU,SE,SK,US

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

   EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
   OA :BF,BJ,CF,CG,CI,CM,GA,GN,GW,ML,MR,NE,SN,TD,TG
   National :AE,AG,AL,AM,AT,AZ,BA,BB,BR,BY,CH,CR,CU,DK,DM,DZ,EE,ES,FI,GB,GD,
   GE,GH,GM,HR,HU,ID,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MW,MX,
   PT,SD,SG,SI,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZW

3. The applicant is reminded that he must enter the "national phase" **before the expiration of 30 months from the priority date** before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing , if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1).

   Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

   The entry into the European regional phase is postponed **until 31 months from the priority date** for all States designated for the purposes of obtaining a European patent.

Th International Bureau f WIPO
34, chemin des Colombettes
1211 G n va 20, Switz rland

Facsimile No. (41-22) 740.14.35

Authorized officer:
Juan Cruz

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

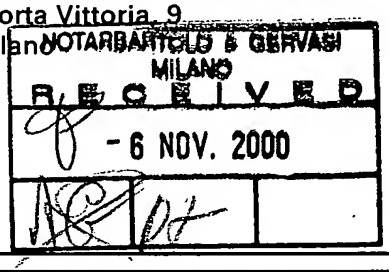
From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
GERVASI, Gemma
Notarbartolo & Gervasi S.p.A.
Corso di Porta Vittoria, 9
I-20122 Milano
ITALIE



Date of mailing (day/month/year)	
26 October 2000 (26.10.00)	
Applicant's or agent's file reference	**IMPORTANT NOTICE**
1805PTWO	

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/EP00/03551	19 April 2000 (19.04.00)	21 April 1999 (21.04.99)

Applicant
EUPHAR GROUP S.R.L. et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AG,AU,DZ,KP,KR,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CN,CR,CU,CZ,DE,DK,DM,EA,EE,EP,ES,FI,GB,GD,
   GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MN,MW,MX,
   NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   26 October 2000 (26.10.00) under No. WO 00/63148

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Gen va 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
J. Zahra

Telephone No. (41-22) 338.83.38

Continuation of Form PCT/IB/308

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

Date of mailing (day/month/year)	IMPORTANT NOTICE
26 October 2000 (26.10.00)	
Applicant's or agent's file reference	**International application No.**
1805PTWO	PCT/EP00/03551

The applicant is hereby notified that, at the time of establishment of this Notice, the time limit under Rule 46.1 for making amendments under Article 19 has not yet expired and the International Bureau had received neither such amendments nor a declaration that the applicant does not wish to make amendments.

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

GERVASI, Gemma
Notarbartolo & Gervasi S.p.A.
Corso di Porta Vittoria, 9
I-20122 Milano
ITALIE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

	Date of mailing *(day/month/year)* 11.05.2001
Applicant's or agent's file reference 1805PTWO	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/03551	19/04/2000	21/04/1999

Applicant
EUPHAR GROUP S.R.L. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Pfitzner, G Tel.+49 89 2399-8032

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
1805PTWO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/03551	19/04/2000	21/04/1999
International Patent Classification (IPC) or national classification and IPC C07C62/36		
Applicant EUPHAR GROUP S.R.L. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
16/11/2000	11.05.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Lorenzo, M.J. Telephone No. +49 89 2399 8239

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/03551

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

4-15	as originally filed			
1-3,3a	as received on	17/04/2001	with letter of	11/04/2001

Claims, No.:

1-5	as received on	17/04/2001	with letter of	11/04/2001

Drawings, sheets:

1/1	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-5
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-5
Industrial applicability (IA)	Yes:	Claims	1-5
	No:	Claims	

2. Citations and explanations
   see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
s e separate sheet

R lt m V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1: US-A-3 366 669 (CHANEZ MARC ET AL) 30 January 1968 (1968-01-30)

D2: WO 98 23574 A (HAN DUCKY ;JUNG JU EUN (KR); KIM DO HA (KR); KIM HEE MAN (KR); KIM) 4 June 1998 (1998-06-04)

1. The present application relates to salts of asiatic and madecassic acid with pharmaceutically acceptable organic bases (claims 1 and 2), pharmaceutical and cosmetic compositions comprising these salts (claim 3) and a process for the preparation of these salts (claims 4 and 5).

2. Document D1 discloses organic salts of asiatic acid, in particular those ones of alkylaminoalkanols and dialkylaminoalkanols and a method for their preparation (see claim 1; column 1, lines 21-27 and 45-47; column 2, lines 26-29 and example 4). These salts are reported to be water soluble; the therapeutic properties of asiatic acid are mentioned and in particular the diethylaminoethanol chlorohydrin salt of asiatic acid is disclosed.

3. Document D2 discloses pharmaceutical acceptable salts of asiatic acid (in particular those ones of alkylamines and heterocycles containing N heteroatoms), their beneficial effect for treating wounds and these derivatives in a gel form (see claims 1 and 2; the examples; experimental example 1 and page 2). The beneficial effects of asiatic acid and madecassic acid in the treatment of skin diseases are reported.

Novelty

4. The subject-matter of claims 1-5 is novel in the sense of Art. 33(2)PCT. Salts of asiatic and/or madecassic acid with the organic bases reported in claim 1 are not disclosed in the available prior art (see paragraphs 2 and 3 herein). Therefore, compositions thereof and a process for their preparation are novel as well.

Inv ntiv st p

5. The subject-matter of claim 1 does not involve an inventive step in the sense of Art. 33(3)PCT.

5.1. The closest prior art (D1 and D2) discloses organic salts of asiatic acid; in particular those of alkylaminoalkanols and dialkylaminoalkanols (see in D1: claim 1; column 1, lines 21-27 and 45-47; column 2, lines 26-29 and example 4) and salts of alkylamines and heterocycles containing N heteroatoms (see the examples in D2).

5.2. The present claimed salts are obtained by using organic bases which consist in a selection from those groups known from the prior art as providing the desired beneficial effects. Such a selection can only be regarded as inventive, if the claimed salts present unexpected effects or properties in relation to the rest of the range. However, no such effects or properties are indicated in the application with respect to the closest state of the art (D1 and D2).

5.3. Hence, no inventive step is present in the subject-matter of claim 1.

6. Dependent claim 2 does not contain any feature which, in combination with the features of claim 1 meets the requirements of the PCT in respect of inventive step. Furthermore, the use of salts of asiatic acid in a gel form is also known from D2 (see paragraph 3 herein). The fact that the present gel composition does not further contain excipients such as those disclosed in D2: propylene glycol, glycol stearate and white petrolatum can only be used for the acknowledged of inventive step is this technical feature produces unexpected effects with respect to the closest state of the art. However, such effects are not reported in the application. Hence, an inventive step cannot be acknowledged (Art 33(3) PCT).

7. Dependent claim 3 does not contain any feature which, in combination with the features of claim 1 meets the requirements of the PCT in respect of inventive step. This claim could only be accepted in combination with a novel and inventive main claim.

8. The subject-matter of claim 4 does not involve an inventive step in the sense of Art. 33(3)PCT.

Document D1 discloses a process for the preparation of salts of asiatic or

madecassic acid with an organic base which is carried out through the same steps disclosed in claim 4. Therefore, an inventive step cannot be acknowledged.

9. Dependent claim 5 does not contain any feature which, in combination with the features of claim 1 meets the requirements of the PCT in respect of inventive step. This claim could only be accepted in combination with a novel and inventive main claim.

Re Item VII

Certain defects in the international application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the description has not been brought into conformity with the amended claims.

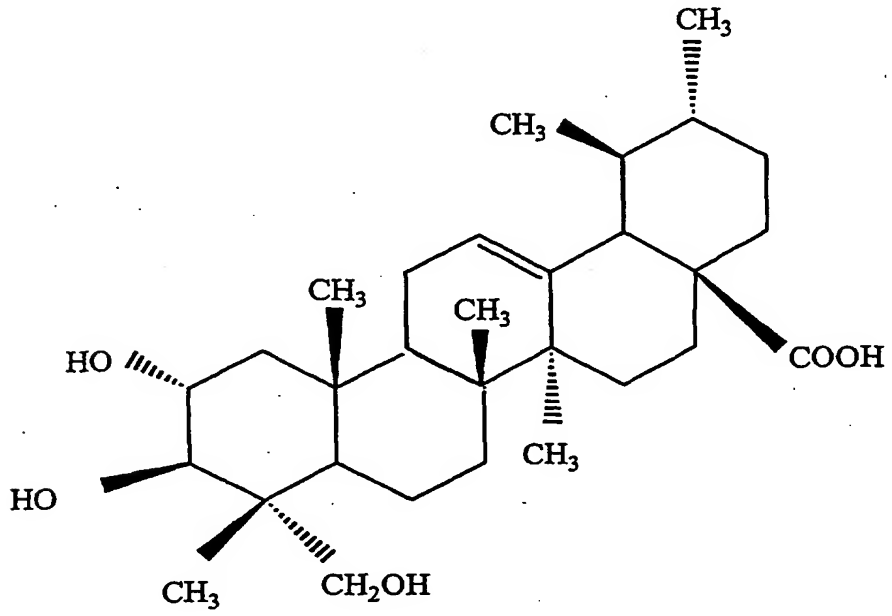
SALTS OF ASIATIC AND MADECASSIC ACID SUITABLE FOR THE PREPARATION OF PHARMACEUTICAL AND COSMETIC COMPOSITIONS

Field of the invention

The present invention relates to the preparation of salts of asiatic and madecassic acid suitable for the preparation of pharmaceutical and cosmetic compositions.

Prior art

Asiatic (2α, 3β, 23 - trihydroxyurs-12-en-28-oic acid) acid (1), madecassic acid (2) and asiaticoside (3) represent the main constituents of the triterpernic total fraction (FTT) of the Centella Asiatica.



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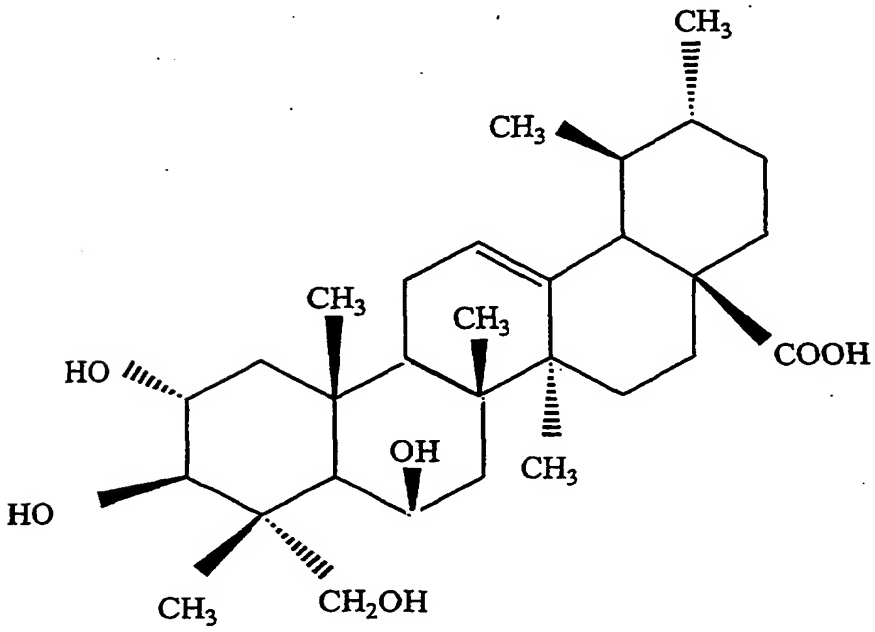

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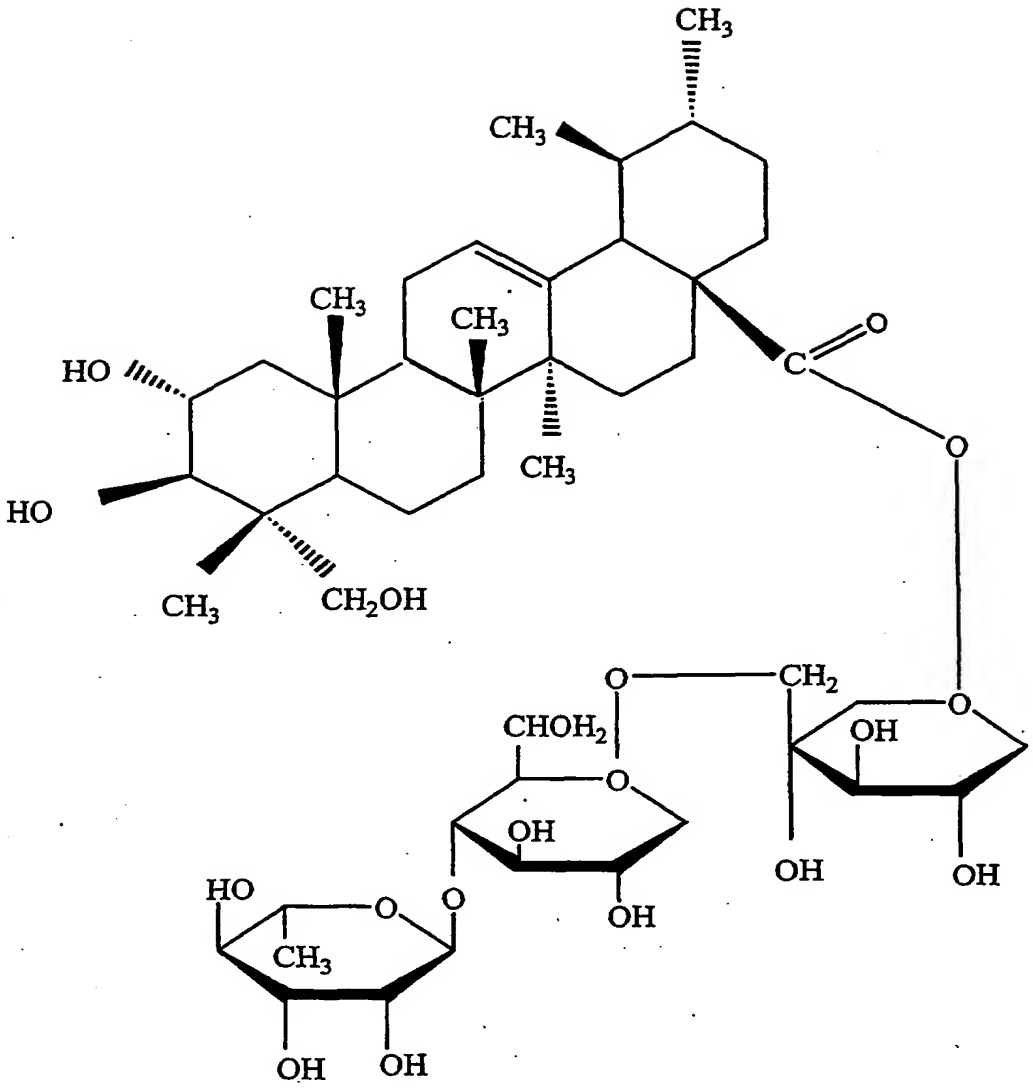

(3)

Digestive, diuretic, reconstituent, cooling, tonic, antipyretic and cicatrizing properties were recognized to said FTT. However the pharmacological interest was mainly focused on the last activity.

In fact it was demonstrated that the FTT of the Centella Asiatica is provided with a peculiar modulating activity on the connective tissue, through an action on the fibroblasts and on two aminoacids fundamental for the metabolism of the collagen: proline and alanine.

All this results in a higher biostimulation of the wound healing processes and in a better reepithelialization.

Therefore, the therapeutic use of FTT of the Centella is tergeted to the treatment

of erithema, varicose ulcers, bedsores, delayed cicatrization, ambustions, traumatic and surgery wounds, systemic and topical inflammatory processes.

The literature data are concordant to consider that the asiatic acid is the most active component of the FTT of the Centella Asiatica in the stimulation of the fibroblasts and consequently in helping the reepithelialization phenomena (F. Bonte, M. Dumas, C. Chaudagne, A. Meybeck. Planta Med. 60, 133, 1994. F.X. Maquart, G. Bellon, P. Gillery, Y. Wegrowski, J. Borcel, Connet Tissue Res. 24, 107, 1990) which however presents considerable problems in the preparation of compositions suitable to topic treatment. Similar problems are encountered with madecassic acid.

In fact, in spite of the presence in their molecular structure of 4 hydrophilic functions (4 hydroxylic groups wherein 3 groups are alcoholic and one is acid), both asiatic and madecassic acid show a poor wettability and an almost total insolubility in water, physico-chemical characteristics which require particular techniques of preparation and particular excipients in the formulation of preparations for topic use, particularly of hydrophilic kind. Furthermore, it is known that the cutaneous absorption mainly happens by transepidermic way (intra - and trans- cellular) and it is mainly controlled by the behaviour of the active principle towards the corneum, mainly formed by keratin and water.

Therefore, in addition to the formulative problems also the problems of a suitable bioavailability of asiatic and madecassic acid at the dermis level remain open (P.-J. Shim, J.-H. Park, M.-Sun Chang, M.-J. Lim, D. Kim, Y.H. Yung, S.-S. Jew, E.H. Pavk, H.-Doo Kim, Bio Organic and Medical Chemistry Letters 24, 2937, 1996).

Organic salts and derivatives of asiatic acid have been disclosed. For example USP N. 3,366,669 discloses hemisuccinates and salts of hemisuccinates of asiatic acid and salts of alkylaminoalkanols and dialkylaminoalkanols of asiatic acid.

Said compounds permit the preparation of aqueous solutions for local uses in therapeutics.

WO98/23574 discloses derivatives of asiatic acid wherein the carboxylic group may be combined with an alkyl group having 1 to 4 carbon atoms, an alkoxymethyl group having 1 to 4 carbon atoms, octyloxymethyl, methoxyethoxymethyl, benzyloxymethyl or 2-tetrahydropiranyl group.

Also a medicine for treating would which comprises said derivatives is disclosed.

Bri f description of the figures

Figure 1 shows the percentage of inhibition of the oedema observed with different doses of Asialene (a) and L-Asialene (b).

Summary of the invention

Now it was found that the problems of the Prior Art may be solved by the salts of the acids of the triterpenic fraction of the Centella Asiatica as, for example, salts of asiatic and madecassic acid with pharmaceutically acceptable organic bases according to the present invention.

In fact, said salts allow:

CLAIMS

1. Salts of asiatic and madecassic acid with pharmaceutically acceptable organic bases, characterized in that said bases are selected from the group consisting of ethylenediamine, ethanolamine, diethanolamine, lysine, benzyltrimethylammonium hydroxide and tetramethylammonium hydroxide.

2. Salts of the asiatic and madecassic acid as claimed in claim 1 characterized in that they are in gel form consisting of said salts and water with a ratio between salt and water ranging from 1:12 to 1:20.

3. Pharmaceutical and cosmetic compositions suitable for topic and systemic treatment of erithema, varicose ulcers, venous insufficiency, bedsores, delayed cicatrization, ambustions, traumatic and surgery wounds, ophthalmic alloeosises, alloeosises of the cutaneous trophism and inflammatory diseases, comprising a pharmaceutically effective or cosmetically idoneous amount of a salt as claimed in claim 1 in mixture with pharmaceutically acceptable or cosmetically idoneous excipient and/or diluent substances.

4. Process for the preparation of salts of asiatic or madecassic acid with pharmaceutically acceptable organic bases as claimed in claim 1, wherein:

a) a solution of said organic base in an organic solvent is prepared;

b) a solution of asiatic or madecassic acid in an organic solvent is prepared;

c) the solution of asiatic or madecassic acid is added to the solution of the organic base;

d) the mixture obtained in the step c) is heated at a temperature ranging from 40 to 70 °C;

e) the solvent is removed and the residue is washed with an organic solvent and crystallized from organic solvent.

5. Process as claimed in claim 4, characterized in that the molar ratio between organic base and asiatic or madecassic acid ranges from 3:1 to 1:1.

SALTS OF ASIATIC AND MADECASSIC ACID SUITABLE FOR THE PREPARATION OF PHARMACEUTICAL AND COSMETIC COMPOSITIONS

Field of the invention

The present invention relates to the preparation of salts of asiatic and madecassic acid suitable for the preparation of pharmaceutical and cosmetic compositions.

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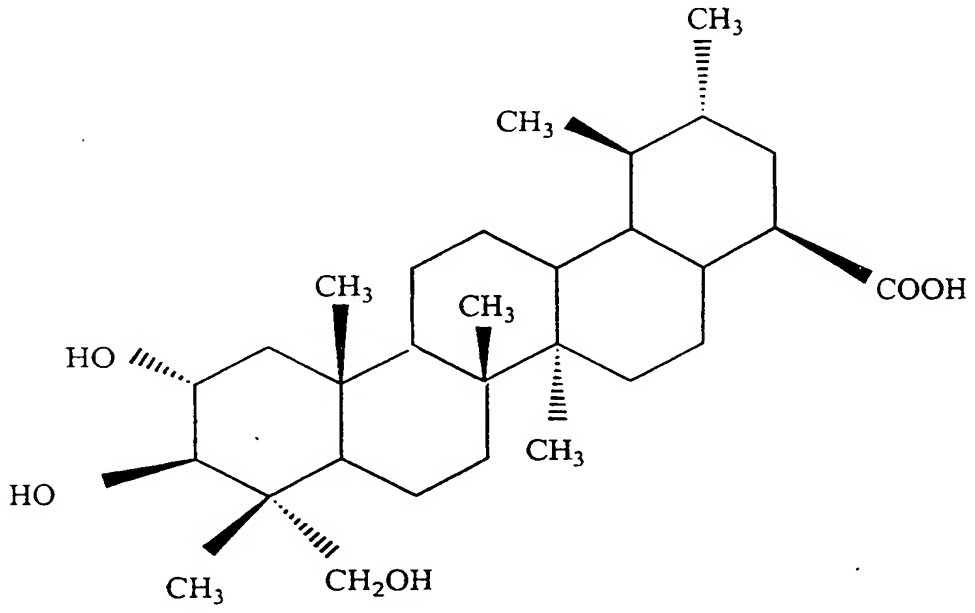

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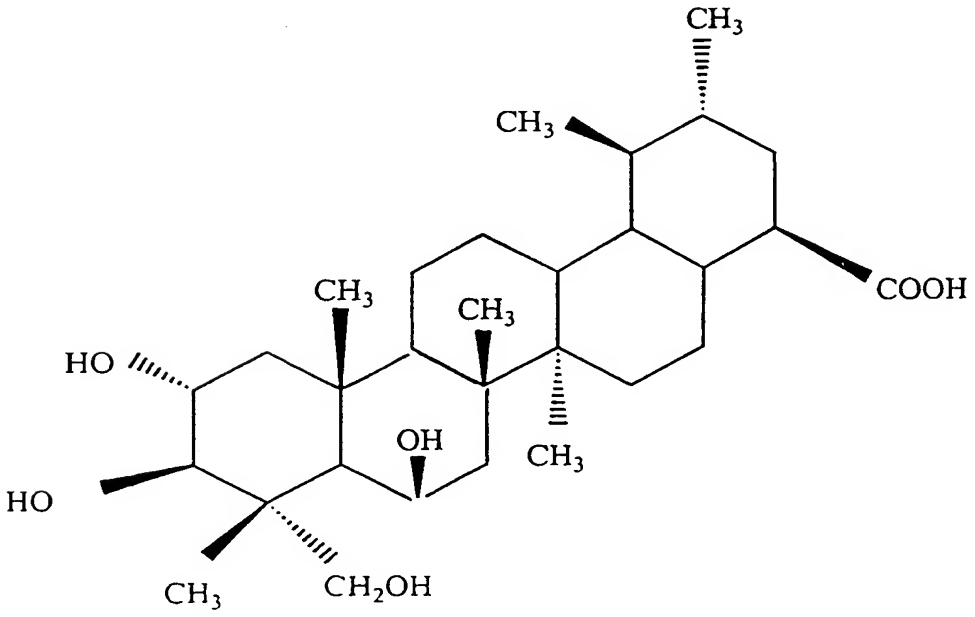

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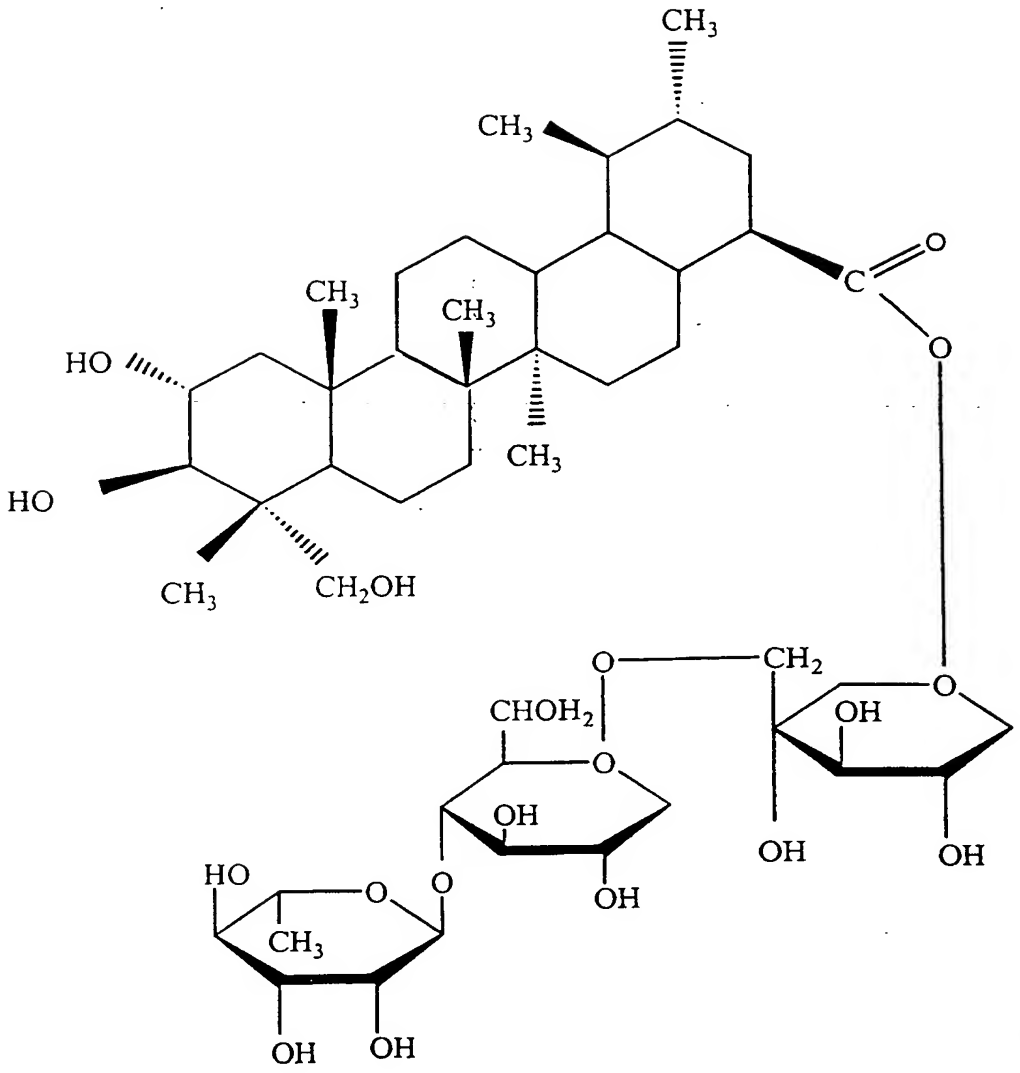

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Now it was found that the problems of the Prior Art may be solved by the salts of the acids of the triterpenic fraction of the Centella Asiatica as, for example, salts of asiatic and madecassic acid with pharmaceutically acceptable organic bases according to the present invention.

In fact, said salts allow:

CLAIMS

1. Salts of asiatic and madecassic acid with pharmaceutically acceptable organic bases.

2. Salts of the asiatic and madecassic acid as claimed in claim 1 characterized in that said organic bases comprise ethylenediamine, ethanolamine, diethanolamine, lysine, benzyltrimethylammonium hydroxide and tetramethylammonium hydroxide.

3. Salts of the asiatic and madecassic acid as claimed in claim 1 characterized in that they are in gel form with a ratio between salt and water ranging from 1:12 to 1:20.

4. Pharmaceutical and cosmetic compositions suitable for topic and systemic treatment of erithema, varicose ulcers, venous insufficiency, bedsores, delayed cicatrization, ambustions, traumatic and surgery wounds, ophthalmic alloeosises, alloeosises of the cutaneous trophism and inflammatory diseases, comprising a pharmaceutically effective or cosmetically idoneous amount of a salt as claimed in claim 1 in mixture with pharmaceutically acceptable or cosmetically idoneous excipient and/or diluent substances.

5. Process for the preparation of salts of asiatic or madecassic acid with pharmaceutically acceptable organic bases as claimed in claim 1, wherein:

a) a solution of said organic base in an organic solvent is prepared;

b) a solution of asiatic or madecassic acid in an organic solvent is prepared;

c) the solution of asiatic or madecassic acid is added to the solution of the organic base;

d) the mixture obtained in the step c) is heated at a temperature ranging from 40 to 70 °C;

e) the solvent is removed and the residue is washed with an organic solvent and crystallized from organic solvent.

6. Process as claimed in claim 5, characterized in that the molar ratio between organic base and asiatic or madecassic acid ranges from 3:1 to 1:1.

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(54) Title: SALTS OF ASIATIC AND MADECASSIC ACID SUITABLE FOR THE PREPARATION OF PHARMACEUTICAL AND COSMETIC COMPOSITIONS

(57) Abstract

Salt of asiatic and madecassic acid with pharmaceutically acceptable organic bases, suitable for the preparation of pharmaceutical and cosmetic compositions for the topic and systemic treatment of erithema, varicose ulcers, venous insufficiency, bedsores, delayed cicatrization, ambustions, traumatic and surgery wounds, alloeosises of the cutaneous trophism, ophthalmic alloeosises and inflammatory processes.

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SALTS OF ASIATIC AND MADECASSIC ACID SUITABLE FOR THE PREPARATION OF PHARMACEUTICAL AND COSMETIC COMPOSITIONS

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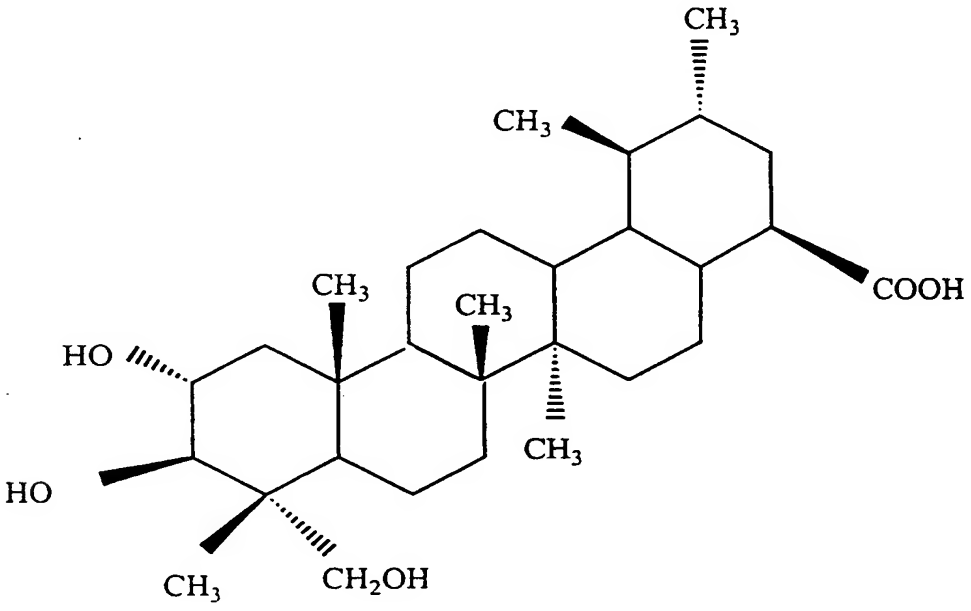

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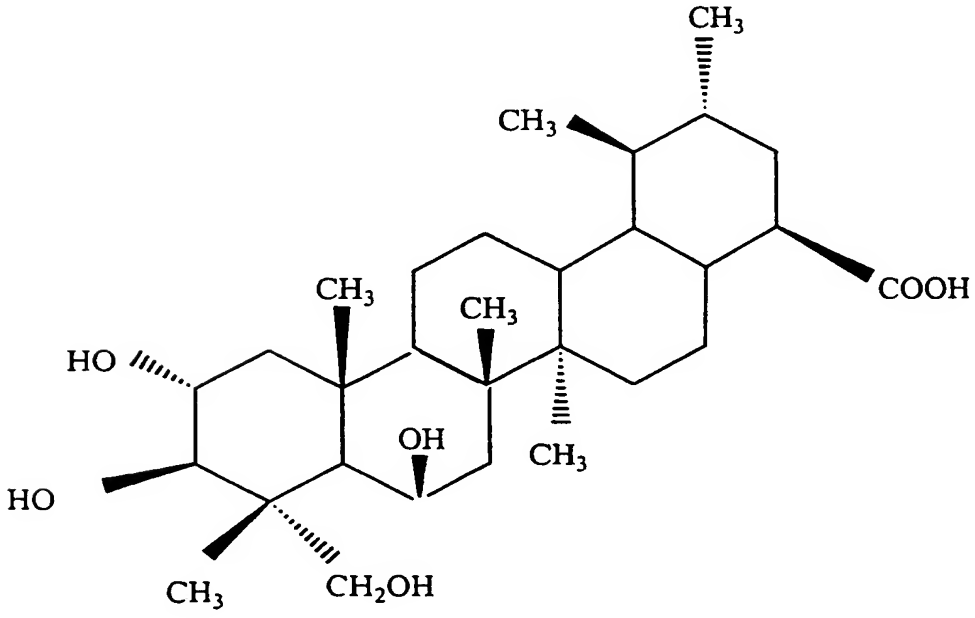

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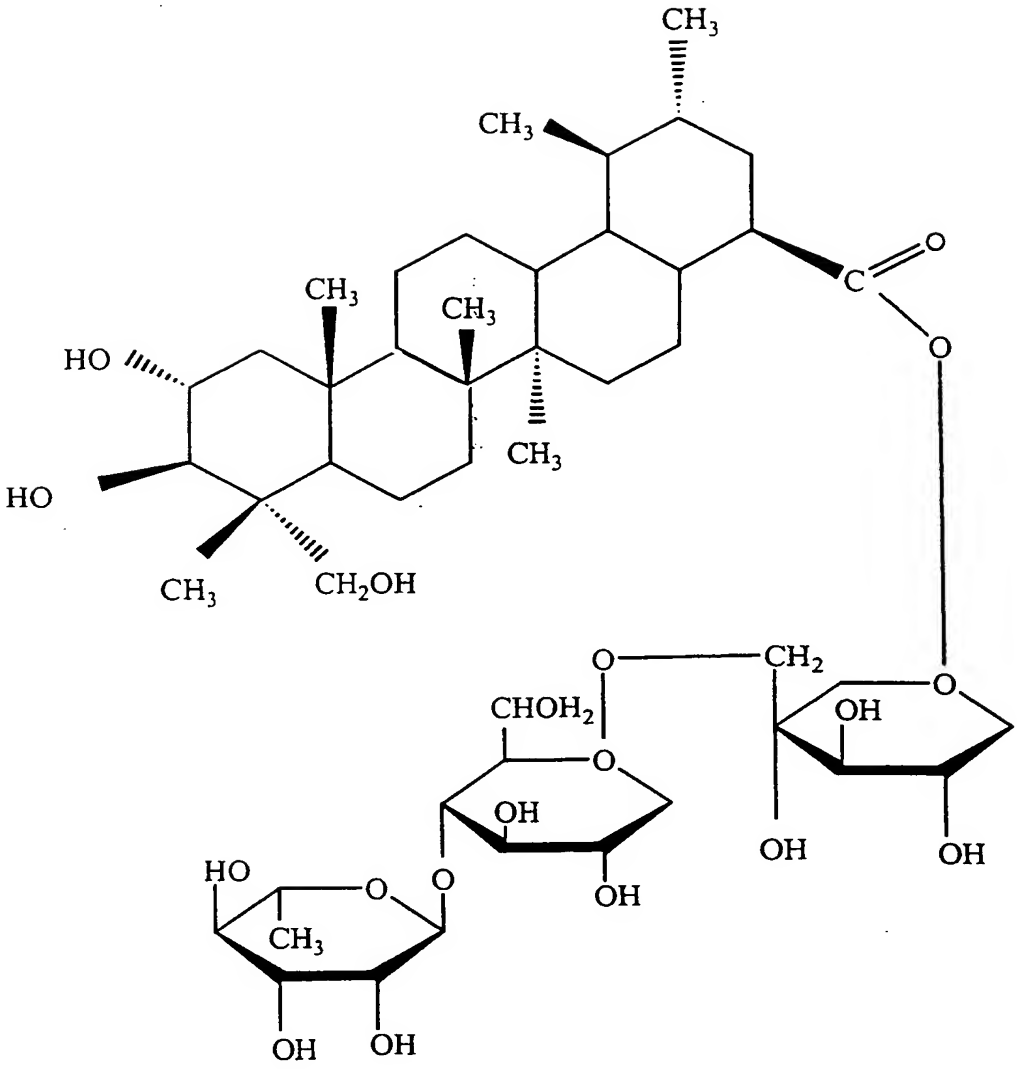

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Therefore, the therapeutic use of FTT of the Centella is tergeted to the treatment

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Brief description of the figures

Figure 1 shows the percentage of inhibition of the oedema observed with different doses of Asialene (a) and L-Asialene (b).

Summary of the invention

Now it was found that the problems of the Prior Art may be solved by the salts of the acids of the triterpenic fraction of the Centella Asiatica as, for example, salts of asiatic and madecassic acid with pharmaceutically acceptable organic bases according to the present invention.

In fact, said salts allow:

a) to prepare easily hydrophilic gels which facilitate the formulation of compositions for topic use;

b) to increase the topic bioavailability of asiatic and madecassic acid at the dermis level; and moreover they are also suitable for the preparation of pharmaceutical compositions for systemic treatment.

These and other characteristics of the salts of asiatic and madecassic acid according to the present invention will be mainly illustrated during the following detailed description.

Detailed description of the invention

The present invention refers to salts of asiatic and madecassic acid with pharmaceutically acceptable organic bases, suitable for the preparation of pharmaceutical and cosmetic compositions.

Said bases include ethylenediamine, ethanolamine, diethanolamine, lysine, benzyltrimethylammonium hydroxide and tetramethylammonium hydroxide.

The preparation of said salts is carried out according to the following steps:

a) a solution of the organic base is prepared in an organic solvent as for example chloroform or ethanol, at room temperature;

b) a solution of asiatic or madecassic acid is prepared in an organic solvent as for example methanol, heating at a temperature ranging from 60 to 80 °C;

c) the solution of asiatic or madecassic acid is slowly added to the solution of the organic base, under stirring at room temperature;

d) the mixture obtained in the step c) is heated at a temperature ranging from 60 to 70 °C for a time ranging from 10 to 30 minutes;

e) the solvent is removed under vacuum at a temperature ranging from 55 to 60 °C;

f) the obtained residue is washed with an organic solvent and then it is crystallized by a suitable organic solvent.

The molar ratio between the organic base and the asiatic or madecassic acid, used in the reaction, ranges from 3:1 to 1:1.

The obtained salts were characterized, besides with the usual analytical methods, as will be reported in the examples, also by infrared spectrophotometry using a PERKIN ELMER 398 spectrophotometer.

The IR (K Br) spectra of the prepared salts show the presence of quite intense bands at about 1540 and 1380 cm-1 attributable respectively to the antisymmetric and symmetric stirring frequencies of the carboxylated group, as a spectroscopic proof of occured salification.

Moreover, a very intense band formed by ammonic and alcoholic bands is observed between 3600 and 3100 cm-1 .

Also some overtones or combination bands in the zone between 2500 and 2000 cm-1 caused by primary ammonic groups are present in the spectra of the salts 4, 5a, 5c, 7 and 8a described in the examples.

The salts according to the invention, when they are treated with water at a ratio by weight between salt and water ranging from 1:12 to 1:20 are able to assume the form of a gel. This property facilitates the preparation of the compositions for topic use with hydrophilic gel.

Moreover said salts allow a modulation of the hydrophilic-lipophylic balance by a suitable choice of the organic base which may exhibit (hydoxylic or α-aminoacids) polar groups or (tetramethyl or benzyltrimethyl) apolar substituents.

The salts according to the present invention have antiinflammatory and cicatrizing effects unexpectedly higher than the total triterpenic fraction (FTT) of the Centella Asiatica and therefore they can be successfully used in the preparation of pharmaceutical and cosmetic compositions for topic treatment of erithema, varicose ulcers, venous insufficiency, bedsores, dalayed cicatrization, ambustions, traumatic and surgery wounds, ophthalmic and cutaneous trophism alloeosises and inflammatory diseases. Moreover, said salts may be used for the preparation of compositions for systemic use, oral and parenteral, with the same therapeutical and cosmetic aims.

Said compositions contain a pharmaceutically effective or cosmetically suitable amount of a salt of the present invention in mixture with pharmaceutically acceptable or cosmetically suitable excipient and/or diluent substances.

The following Examples are reported for illustrative aim of the invention:

EXAMPLE 1

Preparation of the salt of the asiatic acid with ethylenediamine (4)

This preparation is carried out according to the following reaction:

$$2HAs + H_2N\text{-}CH_2CH_2\text{-}NH_2 \rightarrow As^- H_3N^+\text{-}CH_2CH_2\text{-}NH_3^+ As^- \quad (4)$$

wherein the asiatic acid is indicated with HAs. This abbreviation will be also used in the following examples with the same meaning.

A methanolic solution (50 ml) of asiatic acid (4.89 g, 10 mmol) dissolved at a temperature equal to 60 °C is added to a chloroformic solution (30 ml) of ethylenediamine (1.80 g, 30 mmol) at room temperature under stirring and drop by drop.

When the addition is finished, the mixture is heated at 60-65 °C for 20 minutes.

After the removal of the solvents under vacuum, the viscous residue is washed 2 times with ether (30 ml x 2), one time with acetonitrile (30 ml) and finally it is hot crystallized with ethanol (95%). An amorphous white solid is obtained, which crystallizes with two molecules of water. M.p. 311-317 °C.

$C_{62}H_{108}N_2O_{12}$ Calculated: C: 69.37; H: 10.14; N: 2.61

Found: C: 69.16; H: 10.10; N: 2.59

The melting point was determined with a Fisher-John apparatus and the elementary analyses were executed with an EA 1110 elementary analyzer of the FISON INSTRUMENTS S.p.A. society (Milan).

EXAMPLE 2

Preparation of the salts of the asiatic acid respectively with ethanolamine (5a), with diethanolamine (5b) and with lysine (5c)

This preparation is carried out according to the following reaction:

5a - c

5a: R_1 = H, R_2 = CH_2CH_2OH

5b: R_1 = R_2 = CH_2CH_2OH

5c: R_1 = H, R_2 = $(CH_2)_4$-CH-COOH
|
NH_2

A methanolic solution (80 ml) of asiatic acid (4.89 g, 10 mmol) is added at room temperature under stirring to a solution in methanol (80 ml) of the organic base (12 mmol), ethanolamine, diethanolamine and lysine, respectively.

After 15 minutes from the addition, the mixture is heated at 50-60 °C for 20 minutes.

The methanol is removed by vacuum evaporation and the obtained residues are crystallized using suitable solvents, in particular the compounds 5a and 5b are crystallized by methanol-acetone mixtures and the compound 5c by methanol.

The melting points of the three prepared compounds are the following:

5a: 241 - 245°C;

5b: 299 - 305°C;

5c: 300 - 314°C.

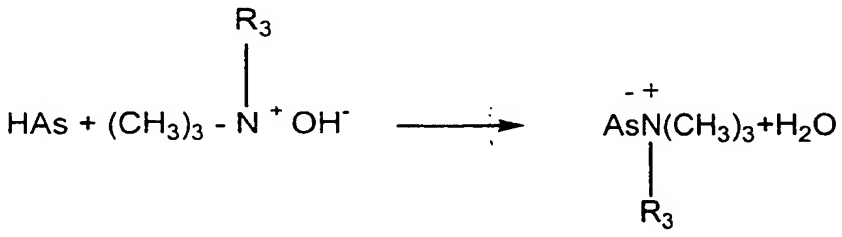
The elementary analyses of the three prepared compounds give the following results:

5a:	$C_{32}H_{59}NO_8$	Calculated:	C: 65.61; H: 10.15; N: 2.39
		Found:	C: 65.41; H: 10.07; N: 2.45
5b:	$C_{34}H_{63}NO_9$	Calculated:	C: 64.83; H: 10.08; N: 2.22
		Found:	C: 64.95; H: 9.98; N: 2.30
5c:	$C_{36}H_{66}N_2O_9$	Calculated:	C: 64.45; H: 9.92; N: 4.18
		Found:	C: 64.65; H: 9.99; N: 4.07

EXAMPLE 3

Preparation of the salts of the asiatic acid with tetramethylammonium (6a) and with benzyltrimethylammonium (6b) hydroxides

This preparation is carried out according to the following reaction:



6 a-b

6a: R3 = CH3

6b: R = C6H5CH2

A methanolic solution (80 ml) of asiatic acid (4.89 g, 10 mmol) is added at room temperature under stirring to a solution in methanol (80 ml) respectively of tetramethylammonium hydroxide and of benzyltrimethylammonium hydroxide (12 mmol).

After 15 minutes the mixture is heated at 50-60 °C for 20 minutes.

The residues obtained after vacuum removal of the methanol are crystallized by suitable solvents, in particular the compound 6a is crystallized by a methanol-acetone mixture and the compound 6b by a methanol-acetonitrile mixture.

The melting points of the two prepared compounds are the following ones:

6a: 214 - 220°C;

6b: 203 - 209°C.

The elementary analyses of the two prepared compounds give the following results:

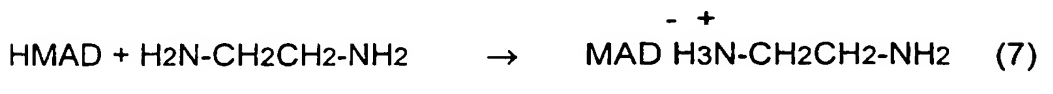
6a: $C_{34}H_{63}NO_7$ Calculated: C: 68.30; H: 10.62; N: 2.34
Found: C: 68.12; H: 10.43; N: 2.38

6b: $C_{40}H_{67}NO_7$ Calculated: C: 71.28; H: 10.02; N: 2.08
Found: C: 71.54; H: 10.21; N: 1.98

EXAMPLE 4

Preparation of the salt of madecassic acid with ethylendiamine (7)

This preparation is carried out according to the following reaction:



HMAD + H_2N-CH_2CH_2-NH_2 → MAD H_3N^+-CH_2CH_2-NH_2 (7)

Wherein the madecassic acid is indicated with HMAD. This abbreviation will be also used in the following examples.

The same procedure as that decribed in example 1 is carried out using, instead of asiatic acid, a methanolic solution (50 ml) of madecassic acid (5.05g, 10mmol).

The salt crystallizes with one molecule of water. M.p. 170-178 °C.

The elementary analysis of the obtained compound gives the following result:

$C_{32}H_{58}N_2O_7$ Calculated: C: 65.95; H: 10.03; N: 4.81

Found: C: 65.66; H: 9.78; N: 4.74

EXAMPLE 5

Preparation of the salt of madecassic acid with ethanolamine (8a) and with diethanolamine (8b)

This preparation is carried out according to the following reaction:

HMAD + HN(R_1)(R_2) → MAD H_2N^+(R_1)(R_2)

8a – 8b

8a: R_1=H, R_2=CH_2CH_2OH

8b: R_1=R_2=CH_2CH_2OH

The same procedure as that decribed in example 2 is carried out using, instead of asiatic acid, a methanolic solution (80 ml) of madecassic acid (5.05 g, 10mmol).

Crystallization is performed in methanol-acetone.

The elementary analyses of the two prepared compounds confirm the following formulas:

8a: $C_{32}H_{58}NO_8$

88: $C_{36}H_{61}NO_9$

EXAMPLE 6

Preparation of the salt of madecassic acid with tetramethylammonium (9a) and with benzyltrimethylammonium (9b) hydroxides

This preparation is carried out according to the following reaction:

9a: R3=CH3

9b= R3=CH2C6H5

The same procedure as that decribed in example 3 is carried out using, instead of asiatic acid, a methanolic solution (80 ml) of madecassic acid (5.05 g, 10mmol).

9a is crystallized in a methanol-acetone mixture and 9b in a ethanol-acetonitrile mixture.

The elementary analyses for the two compounds confirm the following formulas:

9a: C34H61NO7

9b: C41H65NO7

EXAMPLE 7

Preparation of the gel of the salt of the asiatic acid with ethylenediamine

1 g of the salt of the asiatic acid with ethylenediamine, salt (4), prepared as described in the Example 1, is loaded in a flask equipped with a magnetic stirrer.

15 ml of water are then added at room temperature and stirring is begun at a low revolution number (100-150 revolutions per minute).

The water is gradually included in the salt in order to form a gel while the stirring revolution number is gradually increased to 1000-1500 revolutions per minute.

A gel having semisolid consistency is formed in a time equal to 4-6 minutes, which becomes translucent continuing the stirring for 5-8 minutes.

Biological Tests

In order to verify the cicatrizing and platelet anti-aggregation activity of the salts of the present invention in comparison with the products of the prior art, tests reporting the comparison between the salt prepared in Example 1, indicated as Asialene and the total triterpenic fraction of the Centella Asiatica, indicated as FTT, were carried out.

Furthermore, the antiinflammatory activity of Asialene and L-Asialene, the salt of asiatic acid with lysine prepared in Example 2, was evaluated in comparison with that of NSAID indomethacin.

1. Test of production of PG1 and of Fibronectin from human endothelial cells in culture.

The activity of the salt prepared in the Example 1, indicated as Asialene, on cicatrization was evaluated by an in vitro test which allows to deduce the effects of the substance on the vascular permeability and on the cicatrization.

The test consists in the evaluation of the production of PG1 from cells extracted by collagenase from vein of human omphalic funicle suspended and seeded in a suitable culture medium (E199+FCS 20%+L-Glutamine 2 mM+Penicillin 200 U/ml+Streptomycin 200 μg/ml) cultured in 75 or 25 ml flasks for 48-72 hours.

After removing the cells with 0.05% Trypsin and 0.02% EDTA the subcultures were prepared using secondary cultures seeded on a 35 mm Petri dish, kept in an incubator with 5% CO_2 and 100% humidity. For the evaluation of the cell morphology and confluence and the PG1 production, about 300,000 cells/ml of culture medium were used carrying out the count in a Burker chamber, following three schemes:

1. Cells+culture medium+EtOH (0.75 g/dl)
2. Cells+culture medium+EtOH(0.75 g/dl) +FTT(15 μg/ml)
3. Cells+culture medium+EtOH(0.75 g/dl)+Asialene(1.5 μg/ml)

The cultures were evaluated with an inverse light microscope, at 24 and 48 hours monitoring cell attachment and growth while on supernatant aliquots the stable metabolite of the prostacyclin (6-Keto PGF1) was assayed with RIA method.

In the following table the values of 6-Keto PGF1 in μg/ml are reported. (The cicatrizing activity is correlated to the 6-Keto PGF1 levels).

	24 h	48 h
Culture medium +EtOH (0.75g/dl)	415	380
Culture medium + EtOH (0.75 g/dl)+ FTT (15 μg/ml)	520	475
Culture medium + EtOH (0.75 g/dl)+ Asialene (1.5 μg/ml)	980	889

For the Fibronectin evaluation, the primary cultures were resuspended in 0.05% Trypsin/0.02% EDTA. The cells, washed twice in Hanks solution, were counted in order to assure at least 300,000 cells/ml and seeded. After 48 hours the supernatant was removed and the slides were prepared, which after being washed 2 times with PBS, and dried, were fixed in acetic acid/ethanol for 30 minutes; a washing with PBS was then carried out and added the polyclonal rabbit anti-human fibronectin antibody (1:40, Dako). After incubation at room temperature for 30 minutes, it was washed with PBS and the fluoresceinated anti-rabbit immunoglobulin antibody was added (1:100, Dako). The slides were left in incubation for 30 minutes and then mounted on an object holder and read with a fluorescence electronic microscope.

In the following table, the numbers relating to fibronectin intercellular strands (1:100 scale) are reported.

Culture medium +EtOH (0.75 g/dl)	1
Culture medium + EtOH (0.75 g/dl) +FTT (15 μg/ml)	7
Culture medium + EtOH (0.75 g/dl) Asialene (1.5 μg/ml)	85

2. Evaluation of the platelet aggregation inhibiting effect

Blood taken from healthy volunteers not submitted to pharmacological therapy

during one week, was gathered in polyethylene test-tubes containing 3.8% sodium citrate in 1:9 ratio, and centrifuged at 1000 g for 10 minutes in order to obtain plasma having a high platelet content (PRP) and at 3000 g for 15 minutes in order to obtain plasma having a low platelet content (PPP). Two 400 µl PRP samples (300,000 +/- 10000 platelet/ml final concentration) were submitted to incubation at 37 °C for 60 seconds in presence of 100 µl FTT (700 µg/ml) and 10 µl of Asialene (70 µg/ml) respectively. Each sample was divided in three portions which were treated with 10 µl of a platelet aggregation agent, ADP (4mM final concentration), collagen (4µg/ml final concentration) and arachidonic acid (0.2 mg/ml final concentration) respectively, and the aggregation was recorded for 4 minutes.

The obtained results are reported in the following table.

	CONTROLS	FTT 700 µg/ml	ASIALENE 70 µg/ml
Aggregation from collagen (4 µg/ml)	100	70	50
Aggregation from ADP (4 mM)	88	45	32
Aggregation from arachidonic acid (0.2 mg/ml)	81	31	23

3. Test of topical antiinflammatory activity

The antiinflammatory activity of Asialene and L-Asialene was evaluated in comparison to that of the NSAID indomethacin. As experimental model, the Croton oil dermatitis induced in the mouse ear was used (Tubaro et al., Agents & Actions 17: 347-349).

The experimental inflammation was induced on the right ear (surface: about 1 cm^2) of anaesthetised mice (145 mg/kg ketamine hydrochloride i.p.) by application of 80 µg of Croton oil (Sigma – Italy) in 15 µl acetone on the right ear of mice, the left remaining untreated. The tested substances were dissolved in the Croton oil solution. Six hours after the dermatitis induction, the animals were sacrificed and a

punch (6 mm diameter) was excised from both the treated and the untreated ears and weighed. The Croton oil induced oedema was quantified by measuring the difference in weight between the treated and untreated (opposite) ear samples. The anti-oedema activity was expressed as percent inhibition of the oedematous response in animals treated with the test substances in comparison to the animals treated with the irritant alone. Male albino Swiss mice CD-1 (Harlan – Italy), weighing 20-32 g, were used. For each substance and dose level, 10 animals were used.

The effects on the vascular response were evaluated as percent oedema inhibition. Results were analysed by means of the Student's "t" test, accepting as significant a value of p inferior to 0.05. For each substance, the dose level able to reduce by 50% the oedematous response (ID_{50}) was calculated by linear interpolation from the dose-response relationship.

Asialene and L-Asialene were administered at equimolar doses. The obtained results are reported in the following table.

Substance	Dose ($\mu g/cm^2$)	Oedema (mg) m±E.S.	Inhibition (%)
Asialene	0	6.9 ± 0.2	-
	30	5.0 ±0.4*	27.5
	100	2.2±0.5 *	68.1
	300	0.6 ±0.1*	91.3
	1000	0.4 ±0.1*	94.2
L-Asialene	0	7.0 ± 0.4	-
	42	3.9 ±0.7*	44.6
	141	2.6 ± 0.5 *	63.5
	423	0.4 ±0.2*	94.5
Indomethacin	90	3.5 ±0.4*	49.3

* 0.05 at the Student's "t" test

The two products show a strong inhibition of the oedema induced by Croton oil, in a dose-depending way. At the lowest dose tested (30 $\mu g/cm^2$), Asialene provokes a significant oedema inhibition that reaches almost the maximum at 300 $\mu g/cm^2$. As shown in Figure 1, the dose-activity relationship for Asialene represents the higher branch of the classical sigmoid and is linear in the range from 30 to 300 $\mu g/cm^2$, whereas at 1000 $\mu g/cm^2$, the activity lies on the asymptotic part of the curve. From the linear part, an ID_{50} value of 62 $\mu g/cm^2$ can be calculated. L-Asialene shows a practically superimposable effect from which an ID_{50} value of 60 $\mu g/cm^2$ is obtained. Indomethacin, the reference drug, at the dose of 90 $\mu g/cm^2$ inhibits the oedematous response by almost 50%; from past data we can confirm that this dose of indomethacin represents its ID_{50} value.

From the comparison between the ID_{50} values of the tested substances, it can be stated the Asialene and L-Asialene possess pactically the same potency, that appears to be 50% higher than that of the reference drug, at least in this experimental model.

CLAIMS

1. Salts of asiatic and madecassic acid with pharmaceutically acceptable organic bases.

2. Salts of the asiatic and madecassic acid as claimed in claim 1 characterized in that said organic bases comprise ethylenediamine, ethanolamine, diethanolamine, lysine, benzyltrimethylammonium hydroxide and tetramethylammonium hydroxide.

3. Salts of the asiatic and madecassic acid as claimed in claim 1 characterized in that they are in gel form with a ratio between salt and water ranging from 1:12 to 1:20.

4. Pharmaceutical and cosmetic compositions suitable for topic and systemic treatment of erithema, varicose ulcers, venous insufficiency, bedsores, delayed cicatrization, ambustions, traumatic and surgery wounds, ophthalmic alloeosises, alloeosises of the cutaneous trophism and inflammatory diseases, comprising a pharmaceutically effective or cosmetically idoneous amount of a salt as claimed in claim 1 in mixture with pharmaceutically acceptable or cosmetically idoneous excipient and/or diluent substances.

5. Process for the preparation of salts of asiatic or madecassic acid with pharmaceutically acceptable organic bases as claimed in claim 1, wherein:

a) a solution of said organic base in an organic solvent is prepared;

b) a solution of asiatic or madecassic acid in an organic solvent is prepared;

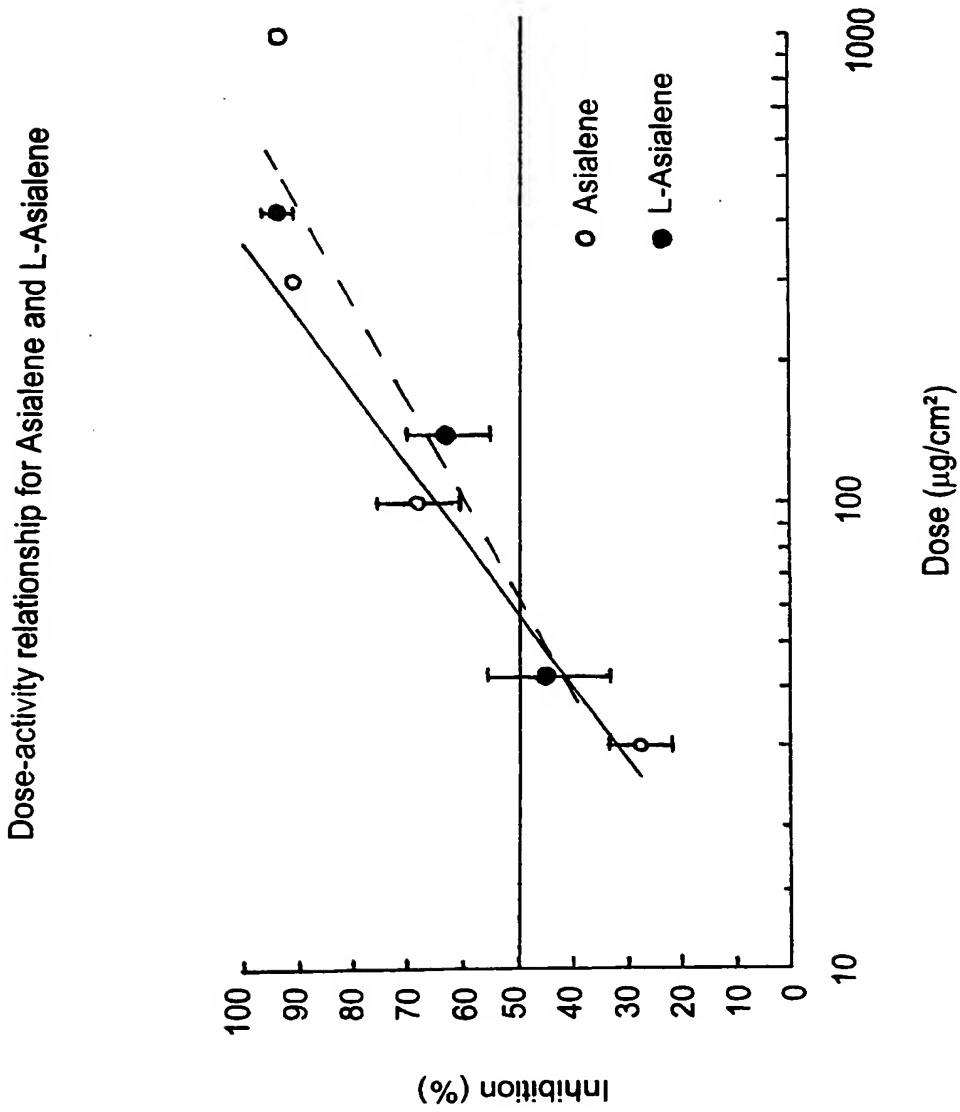
c) the solution of asiatic or madecassic acid is added to the solution of the organic base;

d) the mixture obtained in the step c) is heated at a temperature ranging from 40 to 70 °C;

e) the solvent is removed and the residue is washed with an organic solvent and crystallized from organic solvent.

6. Process as claimed in claim 5, characterized in that the molar ratio between organic base and asiatic or madecassic acid ranges from 3:1 to 1:1.

Figure 1


Dose-activity relationship for Asialene and L-Asialene
Inhibition (%)
100
90
80
70
60
50
40
30
20
10
0
10
100
1000
Dose (µg/cm²)
o Asialene
● L-Asialene

INTERNATIONAL SEARCH REPORT

Int. tional Application No
PCT/EP 00/03551

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C62/36 A61K31/19

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 366 669 A (CHANEZ MARC ET AL) 30 January 1968 (1968-01-30) column 1, line 21-27 column 2, line 26-29 example 4	1,2,4-6
X	WO 98 23574 A (HAN DUCKY ;JUNG JU EUN (KR); KIM DO HA (KR); KIM HEE MAN (KR); KIM) 4 June 1998 (1998-06-04) page 28, line 15 -page 29, line 19 claims 1,2	1,3,4

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 September 2000	25/09/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Delanghe, P

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. tional Application No
PCT/EP 00/03551

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		GB 1067520 A	
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WO 9823574 A	04-06-1998	CN 1238756 A	15-12-1999
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